REMARKS

Entry of the preceding amendments and consideration of the comments which follow are respectfully requested by Applicants.

The office action dated May 15, 2008 has been carefully considered. Claim 1 is amended to clarify that the quality control method related to determining a degree of deprotection of protected groups after synthesis of the biopolymer array is completed so that deprotection steps may be repeated if necessary to insure complete deprotection, in particular of protected amino groups, as disclosed specifically in the instant specification at paragraphs [0017] through [0021] and paragraph [0005]. As this amendment does not involve new matter, entry is believed in order and is respectfully requested.

Claims 1-13 and 15-26 are pending, and claims 1-3, 12, 13, and 15-22 are currently subject to examination.

Rejection under 35 USC §112, first paragraph

Claim 22 is rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. Specifically the Examiner asserts that Claim 22 has been amended to recite "wherein B is selected from the group consisting of adenine (A), guanine (G), cytosine (C), aza analogs, deaza analogs of A, G, and C, combination aza and deaza analogs of A, G, and C and analogs thereof containing additional amino groups" (emphasis added) as filed on 2/18/08, and that this could broadly and reasonably be interpreted to mean analogs of "aza analogs" , analogs of "deaza analogs", etc., which "analogs" of "analogs" do not appear to have support in the instant specification. In addition, the recitation of "combination aza and deaza analogs of A, G, and C" also does not have support of the instant specification. As a result, Claim 22 is considered as representing new matter. This rejection is traversed, and reconsideration is respectfully requested

Applicants note that support for the specific recitation of "combination of aza and deaza analogs" is found expressly at page 9, lines 2-3, which refers back to nucleobases as set forth on page 8, paragraph [0030], first sentence. Further, Applicants note that paragraph [0030] expressly discloses that "nucleobase analogs may carry additional amino groups" (see page 9, line 7). All the recited analogs, such as aza and deaza analogs, are defined in the paragraph as "nucleobase analogs" (see, e.g., "nucleobase analogs are mono- and bicyclic heterocycles comprising at least one amino group....for example, aza analogs..." page 8, [0030] lines 5-8). Hence, it is logically clear that the analogs

themselves, including aza analogs, etc., may carry additional amino groups, and the claim as amended does not present a new matter issue.

Reconsideration is respectfully requested.

Rejection under 35 USC §112, second paragraph

Claims 1-3, 12, 13, and 15-22 are rejected under 35 USC §112, second paragraph, as allegedly being indefinite. Specifically the Examiner notes that claim 1 was amended to recite "carrying out a determination of a degree of deprotection by detecting detectable protecting groups remaining on the array after cleavage," which the Examiner asserts is unclear because it is in conflict with step (b) which step recites "cleaving off the detectable protecting group". The Examiner submits that it is not clear how all the cleaved off "detectable protecting groups" are still "remaining" on the array after cleavage and can be "detected" after the cleavage. The Examiner concludes that one of ordinary skill in the art would not be able to apprise the mete and bounds of the instant invention. This rejection is traversed and reconsideration is respectfully requested.

As amended, claim 1 recites a quality control method for determining degree of deprotection of protected reactive groups in manufacturing of a biopolymer array. The method comprises: (a) synthesizing a plurality of different biopolymer species on an array from monomeric or oligomeric building blocks comprising detectable protecting groups coupled directly to the building blocks, wherein at least some of the detectable protecting groups couple directly to amino groups of the building blocks and remain coupled until synthesis is terminated, (b) after synthesis is terminated, achieving a degree of deprotection by taking one or more steps to cleave the detectable protecting groups, (c) carrying out a determination of the degree of deprotection by detecting detectable protecting groups remaining on the array after cleavage, and (d) repeating steps (b) and (c) if detectable protecting groups are detected, wherein the quality control method is performed on the array.

Applicants submit that the potential for confusion over how one determines a degree of deprotection by detecting groups that were ostensibly all removed in a prior step is overcome by the amendment to claim 1 which clarifies that the quality control method relates to detecting a degree of deprotection and thereafter repeating deprotection steps as necessary until complete deprotection is achieved. Applicants stress that until the present invention as defined by claim 1, to the best of Applicants' knowledge, no other quality control method existed that permitted assessment and redress of degree of deprotection in the context of on-array synthesis, in particular with respect to protected amino

groups wherein deprotection during synthesis is not required, but deprotection at termination of synthesis is absolutely required.

Applicants submit that the instant amendment eliminates the potential for confusion, and the quality control method as presently defined is clear so that the independent claim is definite under §112, and the rejection of claim 1 and claims depending therefrom is overcome. Reconsideration is therefore respectfully requested.

Rejection under 35 USC §103

Claims 1-3, 12, 13, and 15-22 are rejected under 35 USC §103(a) as being unpatentable over US Patent No. 6,238,862 to McGall et al ("McGall") and Wagner et al (Helvetic Chimica Acta. Vol. 80:200-212 ("Wagner"), in view of US Patent No. 5,151,507 to Hobbs et al ("Hobbs") and if necessary, "Chen" et al (Journal of Organic Chemistry, Vol. 66, 1725-1732; 2001, cited previously) and "Agris" (PGPUB 20020045167, 4/18/2002). Specifically, the Examiner asserts that McGall teaches methods of quality control for manufacturing nucleic acid probe arrays, citing to the Abstract and Claim 1, synthesizing nucleic acids using protected monomers, "deprotecting" (or removal) of the protecting group, "determining the amount of unprotected active sites" by detecting the amount of "detectable labels" on the array, wherein the detectable label (or protecting label) is a fluorescent label such as a rhodamine where the fluorescent label is linked (or coupled) to the nucleotide.

The Examiner contends that the instant specification and claims fail to define the phrase "coupled to a nucleobase" so that it may be broadly interpreted to mean coupling the "protection group" (e.g., fluorescent label) and the "nucleobase" through any type of linkage (including both direct and indirect linkage). The Examiner further asserts that since McGall teaches linking the fluorescent label through the phosphate group in the sugar group of the nucleotide, the label is "coupled" to the nucleobase of the nucleotide. The Examiner notes that McGall fails to teach embodiments where the protection groups are directly coupled to and protect the nucleobase amino groups as recited in claim 1.

Wagner is applied for disclosure of methods of nucleic acid synthesis using protected nucleotides where the fluorescent label is linked directly to the nucleobase by coupling through the amino groups and further teaches detecting the protecting groups attached to the synthesized oligonucleotides (e.g., pp.206-207) via a detectable label. The Examiner notes that Wagner teaches hydroxyl and phosphate group protection as well as protecting groups with fluorescent properties.

Agris is applied for assertedly teaching methods of monitoring the degree of deprotection of protected nucleotides on arrays by detecting detectable protecting groups "remaining on the array" and for assertedly teaching the need for such detection so that simple and reliable techniques for determining the purity of the desired oligoncleotides can be carried out (e.g., p. 1, paragraph [0005]). Hobbs is applied for teachings relating to the use of various fluorescent molecules to label (or protect) nucleotides, in particular the use of "stilbene" to attach to the nucleobases through linkers that comprise a "carbonyl" group and for disclosing that various fluorescent dyes can be used depending on the different applications. Chen is applied for teaching that "stilbene" has a "bright fluorescence of very high quantum yield."

The Examiner concludes that it therefore would have been prima facie obvious for one of ordinary skill in the art to attach a fluorescent group such as "stilbene" to a "monomeric building block" (such as a nucleoside) to the amino groups of the nucleobase "for various assays such as detecting the attached fluorescent group on an oligonucleotide array," and one of skill in the art would have been motivated to couple the protection group to the amino group of the nucleobase "because the nucleobase protection groups offer the advantages of providing more efficient and fast working oligodeoxyribonucleotide synthesis," as taught by Wagner. The Examiner further concludes that a person of ordinary skill in the art would have been motivated to directly detect the remaining detectable protecting group on an array to assess the purity of the synthesized oligonucleotides because Agris teaches the need for such as a simple and reliable technique to control the quality of the synthesized microarray, and that it would have been prima facie obvious for a person of ordinary skill in the art to use fluorescent groups (such as stilbene) as the protecting group and to measure the remaining fluorescent signals after cleavage to assess the degree of protection to improve the quality control assay for the deprotection step during an array generation (of methods such as McGall et al) for the predictable result of enabling routine oligonucleotide synthesis on an array with various known protection and labeling groups.

In addressing Applicants' previous arguments, the Examiner objects that Applicants attack the references individually whereas the rejection is based on the combined teachings. The Examiner further objects that certain of Applicants' distinguishing arguments are directed to features not recited (at least expressly) in the rejected claims so that considering them would require improper importation of limitations from the specification into the claims. The Examiner notes Applicants' assertion that Wagner fails to enable the combination of McGall and Wagner because Wagner fails to teach on-chip quality

control analysis but argues that this is irrelevant because McGall teaches on-chip determination of deprotection so that the combination effectively suggests on-chip deprotection.

This rejection is traversed, and reconsideration is respectfully requested.

The recitation of claim1, as amended, is set forth in detail above. In pertinent part, the quality control method of claim 1 requires a determination of a degree of deprotection of protected groups at the termination of synthesis of the biopolymer and repeating the deprotection step as needed if the determination reveals that deprotection is not complete. In particular, claim 1 requires that reactive amino groups on the biopolymer building blocks remain protected until synthesis of the biopolymer is terminated. The instant method permits an on-chip (array) method for assuring complete deprotection of amino groups, which are known in the art for being problematic with respect to complete deprotection. In prior art methods, quality control related assessment of degree of deprotection of amino groups was achieved by assays that relied upon consumption of some of the biopolymer product.

McGall, on the other hand, is directed to methods for quality assessment of biopolymer array synthesis efficiency, not deprotection. McGall labels the 5-OH protecting groups, which must be cleaved at each addition step of the synthetic protocol. McGall does not teach or suggest methods whereby quality of deprotection, in particular of protected amino groups, is determined, remedied, and therefore assured. Instant claim 1 provides a method for determining, redressing and therefore assuring quality of deprotection of reactive groups that are not involved in the synthetic process, but which remain protected until termination of synthesis. This is a completely different problem than efficiency of synthesis, which is not addressed by the instant invention but which is the focus of McGall, and, conversely, McGall fails to acknowledge or address the problem of deprotecting reactive groups not involved in synthesis which must remain until synthesis is terminated. McGall teaches protection of 5-OH, synthesis, deprotection, protection of 5-OH, synthesis, and so on until biopolymer synthesis is complete.

The fact that McGall teaches on-chip quality control of synthesis efficiency is not relevant to the instant method of on-array (chip) quality assurance of complete deprotection of the protected reactive side groups. In order to assess deprotection of amino groups after termination of synthesis, a person of ordinary skill in the art looking for guidance by reference to McGall would not have a reasonable expectation of success and would actually be guided to using known methods for assuring complete deprotection of any side groups which rely on assays that require consumption of bits of the synthesized product.

The Examiner, however, asserts that Wagner overcomes these deficiencies of McGall because Wagner discloses protection and deprotection of both the hydroxyl reactive groups of McGall and the amino reactive groups as instantly required. Further, Wagner teaches assessing the degree of deprotection of all the protected reactive groups. However, as Applicants noted in previous arguments, Wagner adds nothing to the state of the art in quality control methods for ensuring complete deprotection at termination of synthesis occurring entirely on-chip because Wagner, like McGall, relies on off-chip quality control methods relating in particular to determining degree of deprotection, and the motivation arises from synthetic efficiency, not deprotection efficiency.

The Examiner urges Applicants to consider the teachings of McGall and Wagner in combination. Applicants respectfully respond that the Examiner misinterpreted Applicants' argument to come to the conclusion that the references were not considered in toto for all that they disclose. In fact, neither McGall nor Wagner teach quality control methods related to assurance of complete deprotection of all protecting groups used during the synthesis of biopolymer arrays wherein the quality control method is performed entirely on the chip so that consumption of the biopolymer is not required. Applicants draw attention to both critical aspects of the instant methods: first, it is a quality control method relating to assurance of complete deprotection, in particular of protected side groups, such as amine reactive groups, that do not need deprotection during synthesis, but for which deprotection is critical for proper functioning of the synthesized biopolymer; second, it is a quality control method performed entirely on the chip, which confers advantages over known methods performed off-chip. The Examiner insists that the elements argued by Applicants as distinguishing over the art are not recited in the claim. Applicants respond that such a detailed recitation of advantages is not required. The advantages fall directly from the fact that the quality control method is performed entirely on the array/chip. It is not additionally necessary that Applicants recite the ensuing advantages, e.g., that biopolymer need not be removed from the array and consumed as required in prior art quality control methods relating to degree of deprotection.

Applicants note that deprotection at the termination of synthesis is of particular relevance when the biopolymer building blocks comprise, as with oligonucleotide nucleobases, reactive amino side groups that must be protected during synthesis, but which ideally are not deprotected until the termination of synthesis. However, as noted in the instant specification, this presents a problem in the art of on-chip synthesis because it is known that complete deprotection of protected amine reactive groups is difficult to achieve. If synthesis is off-chip, this is less problematic as there are many assays available to assess and remedy this. However, if synthesis is on the array and deprotection is not complete, removal and consumption of some of the synthesized product was considered necessary in order to assess

deprotection efficiency and remedy. Applicants invention as defined by claim 1, however, is the first quality control method for assurance of deprotection of these protected side reactive groups where the quality control method is performed entirely on-chip so that both determination (measurement of label remaining) and remedy (additional deprotection steps) occur on the chip and biopolymer need not be consumed.

McGall teaches deprotection of reactive groups involved in the actual on-chip synthesis which must be deprotected at each addition step. McGall fails to teach or suggest quality control methods relating to assurance of deprotection of groups which do not need deprotection until termination of synthesis. McGall merely relies on the deficient standard in the art sought to be overcome by the present invention whereby quality control assays require consumption of the biopolymer. Wagner teaches protection and deprotection of active amine groups but is irrelevant to on-chip synthesis. Indeed Wagner halts synthesis at various points, removes biopolymer, and assays the product for degree of deprotection. Wagner generates deprotection rates but does not teach or suggest quality control methods for assuring complete deprotection of groups protected during synthesis.

Moreover, Applicants maintain once again that the combination of McGall and Wagner fails to teach, suggest, or enable quality control methods for assurance of deprotection at the termination of synthesis. At most the combination suggests that protection and deprotection of side amine groups may provide valuable data relating to synthesis efficiency of on-chip synthesis. However, for purposes of determining and remedying degree of deprotection, both references suggest reliance on known assays that require consumption of biopolymer.

The tertiary reference, Hobbs, relates to labeled nucleotides useful as chain-terminating substrates for DNA sequencing and teaches stilbene as one such label. Chen, another tertiary reference, discloses specific properties of stilbene as a fluorescent label. Neither of these references addresses quality control methods for determination of degree of deprotection and assuring complete deprotection on-chip (without reliance on assays which require removal and consumption of synthesized product). Agris teaches the importance of assessing and remedying deprotection but fails to disclose anything not already recognized by Wagner and the art in general. Agris merely stands for a well-known thesis – complete deprotection of protected groups may be essential to normal or desired functioning of the synthesized array. Agris fails, however, to teach or suggest methods for achieving this on-chip.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). In order to

render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997). The combination of references applied by the Examiner fails to teach quality control methods for determining degree of deprotection and assuring complete deprotection of protected groups at the termination of synthesis of a biopolymer array where the method is performed entirely on the array as required by instant claim 1. Specifically, the steps of deprotection upon termination of synthesis, determining a degree of deprotection, and running these steps iteratively until complete deprotection is determined, all occurring on the array, are not disclosed by this combination of references. A prima facie case simply has not been established with respect to all the elements of independent claim 1. Hence, claim 1 is nonobvious and patentable under 35 USC §103 over McGall and Wagner, further in view of Hobbs, Chen, and/or Agris.

Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious. *Hartness Int'l, Inc. v. Simplimatic Eng'g Co.*, 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1831 (Fed. Cir. 1987). Hence, claims 2-3, 12, 13, and 15-22, all of which depend either directly or indirectly from claim 1, are likewise nonobvious and patentable over this combination of references. Reconsideration is respectfully requested.

Conclusion

Applicants submit that their application is now in condition for allowance, and favorable reconsideration of their application in light of the above amendments and remarks is respectfully requested. Allowance of claims 1-3, 12, 13, and 15-22 at an early date is earnestly solicited.

The Commissioner is hereby authorized to charge any fees associated with this Amendment to Deposit Account No. 02-2958.

Respectfully submitted,

Marilyn L. Amick
Reg. No. 30,444

Customer No.: 23690
Phone: 317-521-7561
Fax: 317-521-2883